## REMARKS

This response is in reply to the final Office Action dated November 26, 2004. Claims 1, 2, 5-7, 9-12 and 21-25 are pending and under consideration.

## I. CLAIM REJECTION UNDER 35 U.S.C. § 102(e)

Claims 1-2, 5-7, 9, 10, 12 and 21-24 stand rejected under 35 U.S.C. § 102(e), allegedly as being anticipated by U.S. Pregrant Publication 2004/0106108 by Grenier *et al.* ("Grenier *et al.*"). Applicants respectfully transverse.

Applicants submit herewith a Declaration of Gary P. Schroth under 37 C.F.R. § 1.131 ("Declaration") to remove Grenier *et al.* as § 102(e) art. Applicants respectfully request that the Patent Office enter and consider the Declaration of Gary P. Schroth. The Declaration was not previously presented because Grenier *et al.* was not previously cited by the Patent Office under any § 102(e) rejection.

Grenier *et al.* was filed October 15, 2001, claiming priority from U.S. Provisional App. No. 60/239, 259 filed May 22, 2001, which is a continuation-in-part of U.S. App. No. 09/861,292, filed May 18, 2001, which claims priority from U.S. Provisional App. No. 60/282,831, filed April 10, 2001, and from U.S. Provisional App. No. 60/240,397, filed October 14, 2000. Thus, the earliest *possible* effective filing date of Grenier *et al.* is October 14, 2000.

Applicants respectfully submit that this Declaration, particularly the Exhibits associated with the Declaration, establishes conception of the subject matter of the instant claims prior to October 14, 2000, coupled with due diligence from prior to October 14, 2000, to a subsequent reduction to practice of the claimed subject matter and/or until the March 1, 2002, filing date of the instant application.

Exhibit A of the Declaration demonstrates that the Dr. Schroth conceived the subject matter of the pending claims prior to October 14, 2000. Exhibit A is a copy of an Invention Disclosure Form submitted by Dr. Schroth to the legal department of PE Corporation/Applied Biosystems, the original assignee of the instant application. The dates were redacted in accordance with the standard practice (*See* M.P.E.P. § 715.07) but are prior to October 14, 2000. As shown in the Invention Disclosure Form, prior to October 14, 2000, the inventor had conceived methods of identifying a coded test unit in a plurality of coded test units and methods of decoding a plurality of coded test units, comprising, *inter alia*, contacting the coded test units with a decoding oligonucleotide comprising an orthogonal nucleobase. Orthogonal oligonucleobases were referred to as "AEGIS bases"; decoding

oligonucleotides were referred to as "labeled complements" in the Inventor Disclosure Form. *See* Declaration, ¶¶ 5-6.

Exhibits B-H of the Declaration demonstrate due diligence from prior to October 14, 2000, to a subsequent reduction to practice of the claimed subject matter and/or until March 1, 2002, the filing date of the instant application. For example, Exhibit B shows that prior to October 14, 2000, the Invention Disclosure Form (Exhibit A) was delivered to outside counsel for preparation of the instant patent application. *See* Declaration, ¶ 8. Further, Exhibits C-H show that inventor's outside counsel were diligently drafting, seeking comments, revising, finalizing and filing a patent application for the instant invention from prior to October 14, 2000, to March 1, 2002. Particularly, Exhibits C, D, E and G evidence that various drafts of the instant application were prepared and submitted for review from the inventor's outside counsel to in-house patent attorneys at Applied Biosystems. *See* Declaration, ¶¶ 9-12. Exhibit F evidences that the inventor and in-house patent attorneys were reviewing, making comments on draft applications and sending comments to outside counsel for revising the draft application. *See* Declaration, ¶ 13. In addition, Exhibits D, E and G evidence several conversations regarding various drafts and revisions of the instant application between the inventor's outside counsel and in-house patent attorneys at Applied Biosystems, during the period between October 14, 2000, and March 1, 2002. *See* Declaration, ¶¶ 11, 12 and 14.

Taken together, the works and acts evidenced by the documents of Exhibits A-H establish conception prior October 14, 2000 coupled with due diligence from prior to October 14, 2000, to a subsequent reduction of the rejected claims and/or until March 1, 2002, the filing date of the '411 Application. Thus, the Declaration establishes invention of the subject matter of the rejected claims prior to the earliest possible effective filing date of Grenier *et al.* in accordance with 37 C.F.R. § 1.131 and M.P.E.P. § 715. Grenier *et al.* is therefore not prior art under 35 U.S.C. § 102(e).

Accordingly, Applicants respectfully request the rejection under 35 U.S.C. § 102(e) be withdrawn.

## II. CLAIM REJECTION UNDER 35 U.S.C. § 103

Claims 11 and 25 stand rejected under 35 U.S.C. § 103 as allegedly being obvious over Grenier *et al.* in view of Cronin *et al.*, Human Mutation, vol. 7, pages 244-55, 1996 (Cronin *et al.*). Applicants respectfully transverse.

Applicants respectfully remind the PTO that the burden is on the PTO to establish a *prima facie* case of obviousness, which requires the PTO to show that that the reference or combination of references teaches or suggests each and every element of the claims. M.P.E.P. §§ 2142-43. As demonstrated above and in view of the Declaration of Gary P. Schroth Under Rule 1.131, Grenier *et al.* is not prior art to the present invention. Therefore, Grenier *et al.* cannot be combined with Cronin *et al.* to cure the deficiencies of Cronin *et al.* and arrive at the claimed invention.

Applicants submit that Cronin *et al.* does not teach or suggest Claims 11 or 25. In particular, Cronin *et al.* fails to teach or suggest methods of identifying a coded test unit in a plurality of coded test unites or methods of decoding a plurality of coded test units, comprising, *inter alia*, contacting the coded test units with a decoding oligonucleotide comprising an orthogonal nucleobase. Indeed, Cronin *et al.* teaches away from the present invention by requiring specific geographical arrangement of capture oligonucleotides based on sequence. Thus, the Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness.

Accordingly, Applicants respectfully request the rejection of Claims 11 and 25 under 35 U.S.C. § 103 be withdrawn.

## CONCLUSION

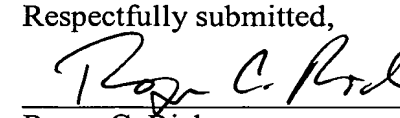
Applicants respectfully request that the foregoing remarks and the Declaration of Gary P. Schroth be made of record in the file of the above-identified application.

Applicant submits that the claims as presently pending meet all of the criteria for patentability and are in condition for allowance. Early notification to this effect is earnestly solicited.

No fees, other than that for a Petition for Extension of Time, are believed due with this response. However, the Commissioner is authorized to charge any fees under 37 C.F.R. § 1.17, any underpayment of fees, or credit any overpayment Jones Day Deposit Account No. 503013 (order no. 103639-999029) that may be required by this Amendment and Response.

Respectfully submitted,

Date: **MAY 23, 2005**



54,398

Roger C. Rich (Reg. No.)

For: Samuel B. Abrams (Reg. No. 30,605)

**JONES DAY**
222 East 41st Street
New York, New York 10017-6702
(212) 326-3939

PE CORPORATION
PE BIOSYSTEMS DIVISION



Disclosure No. 4617

# INVENTION DISCLOSURE FORM



1. **Suggested Title of Invention:**

**Use of AEGIS bases for decoding (and beyond)**

2. **Suggested Inventor(s):** [Include first name, middle initial, and last name, phone extension, mail stop, home address and citizenship. Please specify if named person is not an employee of PE Biosystems. Final inventorship will depend on patent claims]:

Gary P. Schroth
Extension 2436, MS-446
687 Beach Park Boulevard
Foster City, CA 94404

Citizen of USA



3. **Invention Data**

***** See attached pages for the following information **********

A) **Background of Invention.** Provide a brief description of the background of the invention, including citation of any related publications helpful to understanding the field of the invention.

B) **Description of Invention.** Provide a detailed description of the components of the invention, including all major structural or functional components of a new device or composition, the main steps of a new method, how the invention can be made or performed (drawings are welcome), and any representative data.

C) **Advantages.** List advantages of and/or problems solved by the invention.

D) **Potential Product Applications.** Indicate how the invention relates to present or future Company products.

4. **Publication**

**Have any of the following events occurred, or are any expected in the near future? For "yes" items, provide details, date(s), and/or any impending deadline(s).**

Yes ☐ No ☒ Submission of abstract, protocol or manuscript for publication (e.g., for research journal, public meeting, user bulletin, product brochure, posting on the web, etc.).

Yes ☐ No ☒ Actual publication in any format, or written disclosure to a third party outside PE Biosystems (indicate if covered by confidentiality agreement).

Yes ☐ No ☒ Demonstration of invention to anyone outside PE Biosystems (e.g., at trade show).

Yes ☐ No ☒ Offer of donation, loan, license, or sale of invention or product made using the invention.

Yes ☐ No ☒ Other possible public disclosure.

## 5. Government Assistance or Funding

Yes ☐ No ☒ Was the invention developed under a Government contract or subcontract, or supported by Government funds? (If yes, please explain)

## 6. Signatures And Witnesses

**Signatures of Suggested Inventor(s):**

(Signed) (Date)

(Signed) (Date)

(Signed) (Date)

(Signed) (Date)

**THIS FORM MUST BE WITNESSED**
**Witnesses (I have read and understood the foregoing invention disclosure on the date indicated next to my name):**

(Signed) Date

(Signed) Date

Legal Department (Patent Group) Date

*Notes to Invention Disclosure Form:*

* *For assistance with this form, please contact Patti Selan (6179), Paul Grossman (5846), Scott Bortner (6245), Vince Powers (6492) or Alex Andrus (5607).*
* *Please return completed form to Patti Selan, Legal Department, M/S 432-2, 850 Lincoln Centre Drive, Foster City, CA 94404.*
* ***Promptly notify the Legal Department of any changes or improvements made after submission of disclosure by submitting written description and/or drawings describing the improvement. Please note the assigned disclosure number on your written materials.***

## Background of Invention

One of the unique features of Illumina's bead array technology is that the beads are randomly assembled into arrays. This gives the platform a strategic advantage in terms of intellectual property compared to other systems used by other companies. The disadvantage of this method, however, is that each individual array must be "decoded" in order to correlate every bead position with a defined probe. This is known as the decoding process. Illumina has proposed a process for decoding our ZipCode arrays that involves using all of the fluorescently labeled complements to the ZipCode oligos and then hybridizing these onto the array sequentially as groups, or pools, of oligos. In order to decode a 2000 feature array with a two-color decoding scheme, the arrays have to be hybridized, washed, and re-hybridized 10 or 11 times.

My prediction is that this hybridization-based decoding process is going to be fraught with problems of specificity, especially cross-hybridization between different codes on the array. In fact, the array group has already observed significant cross-reactivity between ZipCodes in optimized hybridization reactions at relatively low target concentrations (<<1 nanomolar). Illumina has proposed that, in order to speed up the manufacturing of the beaded arrays, the decoding process will be done with highly concentrated oligos (>>1 nanomolar) coupled with very fast hybridization times. It is easy to imagine that at such high concentrations of labeled oligos it will be very difficult to accurately decode even modestly large sets of beads (e.g. 2,000 different beads in a total array size of 50,000 features) because of the confounding effect of cross-hybridization.

Even if a decoding process can be worked out for a set of 2,000 different ZipCode beads, this process will not necessarily be transferable to any other bead sets. Since our intent is to eventually use the Illumina system for gene expression profiling, we must have a more flexible and universal solution for decoding many different bead sets. This disclosure proposes a chemical solution to increase the specificity, and therefore the efficiency and accuracy, of the decoding process. This method is also "universal" in that the decoding process is independent of the assay or application. In other words, this process could be used to decode beads for both genotyping arrays and any type of gene expression arrays that we develop in the future.

## Description of Invention

The basic outline and features of this invention are described in the attached set of figures. The AEGIS bases have been developed by EraGen Biosciences, and I have been part of a PEB team that has been interested in using this technology to create novel applications. AEGIS bases are non-Watson-Crick (WC) bases that can be incorporated into nucleic acids to create novel base pairing schemes. The two new base pairs shown in the figures are Iso-C paired with Iso-G, and Xanthine paired with Kappa. AEGIS bases can theoretically be incorporated in DNA, RNA, LNA, PNA, or any other nucleic acid

backbone. DNA that contains both AEGIS bases and WC bases behaves very much like standard WC DNA, except that these molecules have expanded "information content" relative to DNA. This means that for any given length there are more possible sequences available when you have 6 or 8 bases to choose from compared with only 4 in standard WC-DNA. This phenomenon can be used to our advantage in situations where cross-hybridization of oligonucleotides is a problem, such as in decoding of beads.

An added benefit of using AEGIS bases in an addressable array is that the array will have less non-specific hybridization with labeled nucleic acids that are created in the assay. Of course all naturally occurring DNA or RNA will not contain AEGIS bases and therefore will not specifically hybridize to the decoding region of the bead. This aspect of the AEGIS technology could be applicable to other ongoing and future projects with PEB. I have listed some of the PEB projects that could potentially benefit from the use of AEGIS bases in one of the figures.

As shown in the figures, the AEGIS containing decoding domains and the target specific domains could be on separate oligos (Scheme 1) or could be part of the same oligo (Scheme 2). I favor the method shown in Scheme 2, since it would probably be easier to implement and control. Because there is so much more complexity in WC-AEGIS-DNA compared to WC-DNA, the decode oligos made with AEGIS bases could be significantly shorter than the 24-mers used in the ZipCode assay. Our best estimates are that an array of 14-18 bp oligonucleotides containing all eight bases (A, C, G, T, Iso-C, Iso-G, K, and X) would have much less cross-reactivity than an array of 24 bp ZipCode oligos containing only A, C, G, and T.

Finally, it should be mentioned that some very strong proof-of-concept data supporting these ideas can be found in Chiron's branched-DNA (b-DNA) product development process during the past 5 or 6 years (see last figure). The b-DNA assay is a signal amplification process that is based upon a very complex web of DNA hybridization events, that essentially builds a "christmas tree" of signaling probes on every target molecule. When this assay was first introduced it had a sensitivity of detection about 10,000 copies of HIV genomes per ml of blood, and debilitating problems with non-specific hybridization which caused high background. After a few years they began using Iso-C and Iso-G bases in their signaling probes and were able to dramatically lower non-specific binding and background. With these improvements in hybridization performance the overall sensitivity of the assay improved to about 100 copies of HIV genomes per ml of blood. This improvement was accomplished by using a total of 6 bases compared with only 4 in WC-DNA, with eight different bases the effect would have be even greater. (Chiron apparently will be licensing the use of Iso-C and Iso-G for EraGen once the EraGen patents are issued.)

## Advantages

1) The use of AEGIS bases may be the only feasible way to accomplish any hybridization-based decoding scheme. It is still not clear to me that decoding can be done on 2000 beads using only WC-DNA.

2) The proposed methods are universal. The same decoding method could be used for decoding a set of 2000 beads for gene expression or genotyping assays. This obviously would help in the manufacturing process if there were only one procedure required for any combination of beads. *We do not want to have to re-develop a decoding process for every new assay that is developed for the Illumina system!*

3) The decoding domains of the beads will have much less cross-reactivity with naturally occurring DNA or RNA samples, which will lead to improved assay backgrounds.

4) We could eventually have qualified manufacturing processes for a few different sized bead pools. For instance, we may have a separate protocol and procedure for 1,000 or 2,000 or 10,000 bead sets.

## Potential Product Applications

The most obvious product application for this method would be for decoding custom bead sets for analysis on the Illumina array system that we are developing in Synthesis and Arrays. Currently we are developing a decoding system that will, at best, only work for decoding ZipCode arrays. These methods will improve that process plus allow for the creation of custom bead sets that will be very valuable for gene expression assays. I have also listed many other projects/products that are being developed at PEB that may be able to benefit from the use of an expanded genetic code.

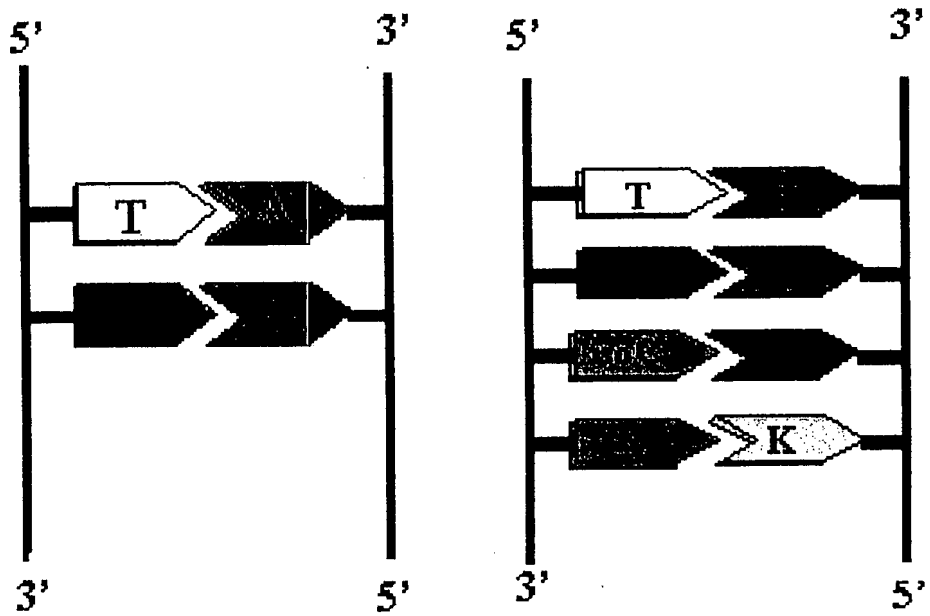
# Use of AEGIS bases for decoding (and beyond)

*Figures for Invention Disclosure*

*Gary P. Schroth*
*Synthesis and Arrays*
*May 19th, 2000*

# AEGIS: An Expanded Genetic Information System

AEGIS bases increase the "information content" per length of oligo

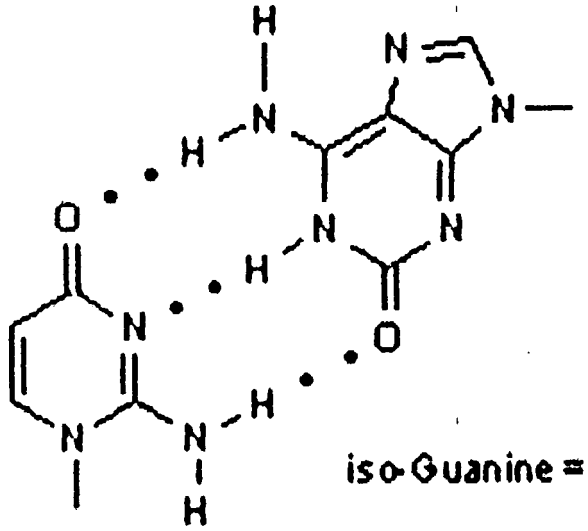



for more information visit www.eragen.com

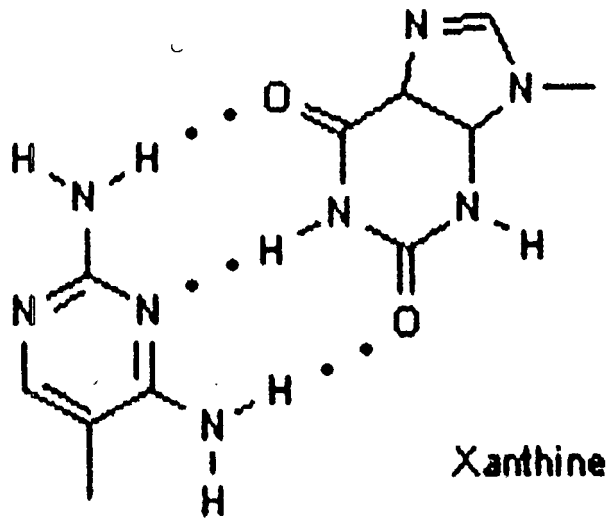
## For instance, in a 10-mer probe:

**There are ~1,000,000 unique sequences in DNA, but about**

**1,000,000,000 unique sequences using this AEGIS code**



iso-Guanine = iso-G



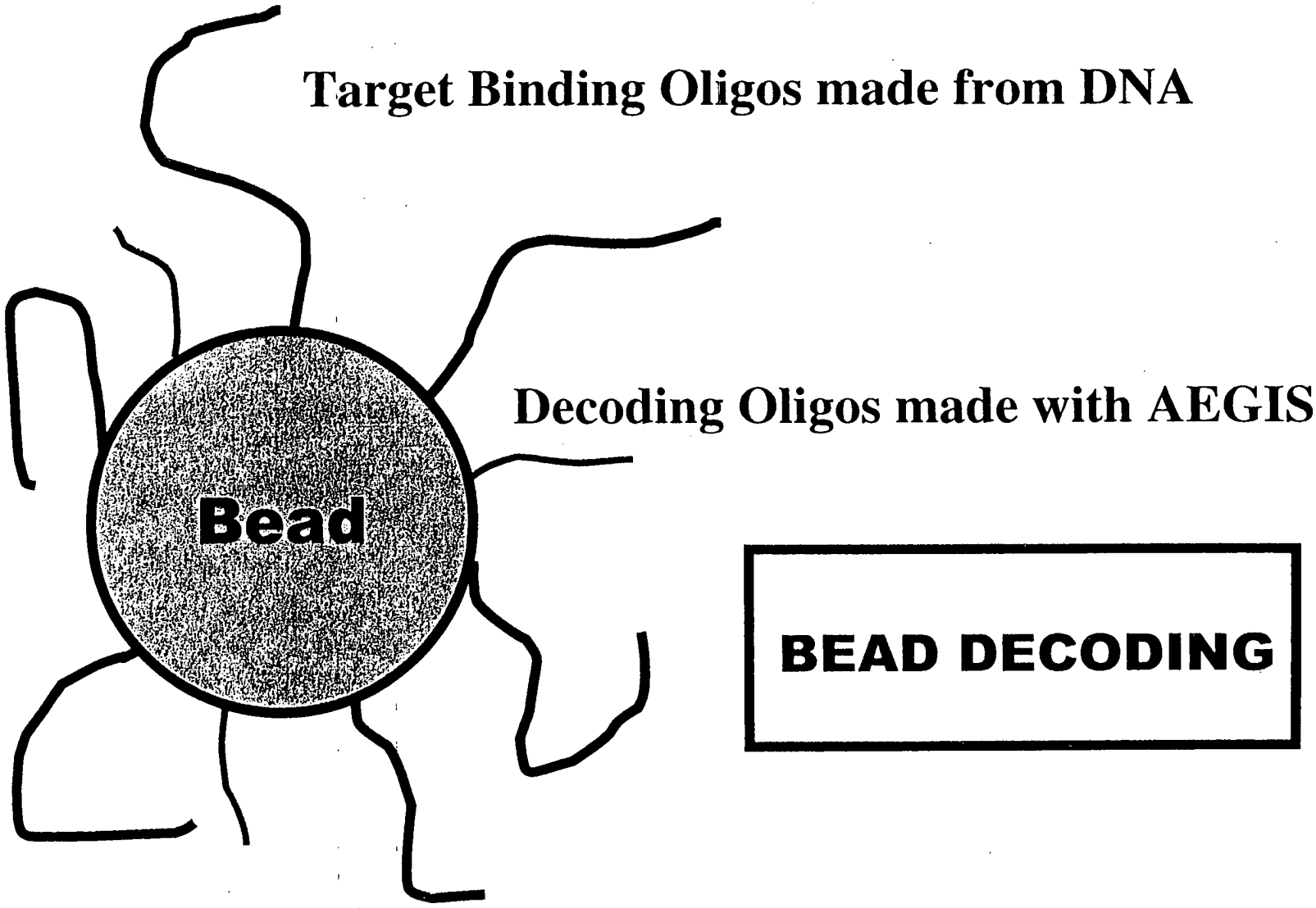
Xanthine = X

iso-Cytosine = iso-C

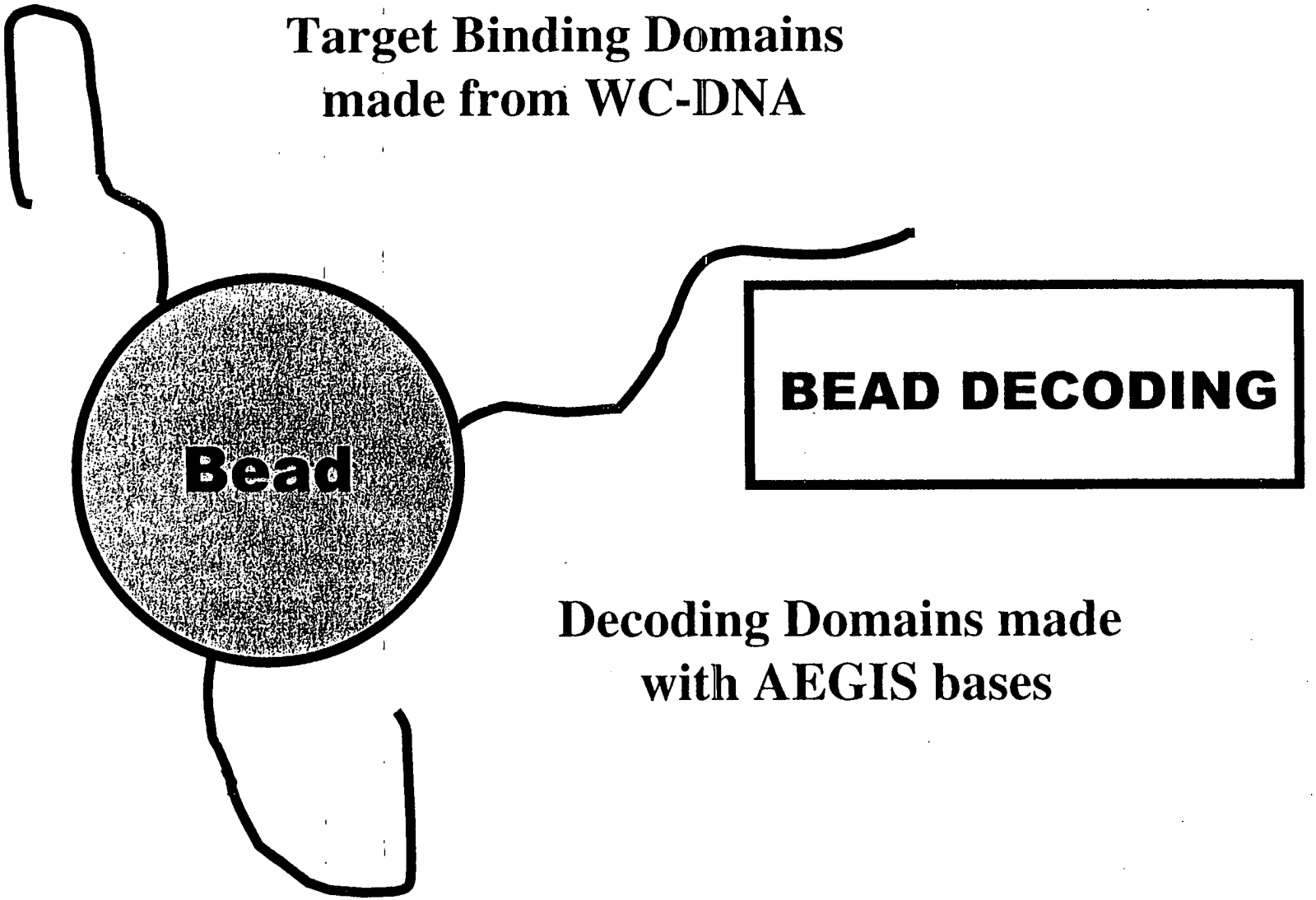
Kappa = K

for more information visit
www.eragen.com

# AEGIS base pairing schemes




**Scheme 1: AEGIS Bases can be used in separate decoding oligos**



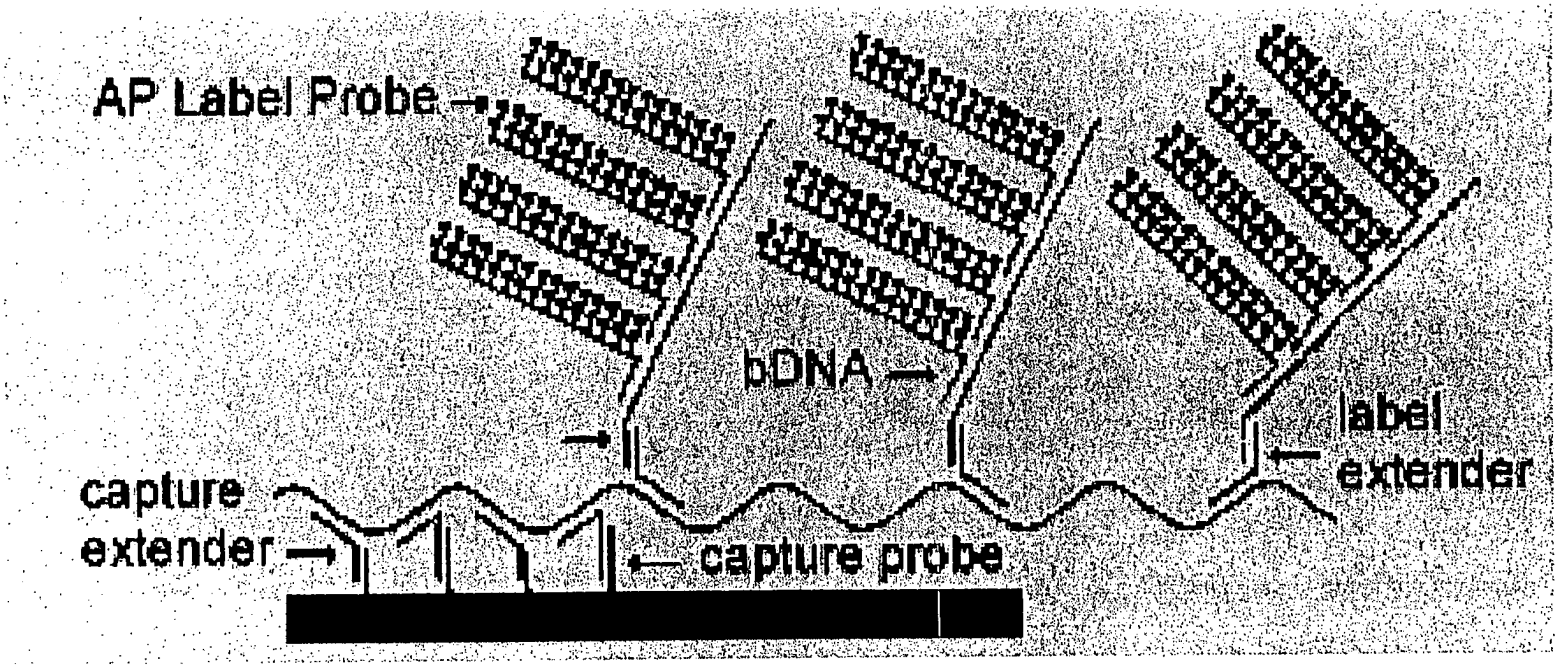

**Scheme 2: AEGIS can be used in Decoding Domains of one oligo**

## Advantages of Using AEGIS for Decoding Beads

- AEGIS bases will make any hybridization-based decoding scheme more specific and efficient.
- These schemes could be "universal", i.e. independent of the assay or application (which is defined only in the target binding regions shown in the two diagrams).
- The decoding regions will not cross-hybridize with DNA or RNA sequences present in biological samples.
- It is easy to imagine creating universally decoded bead sets in sizes of 2000, 5000 or 10000 for use with any target, in any assay or application.

## Other Proposed Uses For AEGIS in PEB projects

- Marking of assembled arrays to give a unique identifier for each array cluster (positive hybridization control).
- Novel sequences for Zipcodes for OLA-PCR assay
- Improve specificity of PNA-PNA or PNA-DNA duplexes
- Improve specificity of Hybridization Based Pullout (HBP)
- Possible use as "flap" sequences in TWT Invader assay
- For signal amplification of hybridized target on DNA arrays ("Christmas" tree effect)




**Strong proof-of-concept data comes from Chiron's branched-DNA (b-DNA) system, which was originally plagued by high background due to non-specific hybridization. By using Iso-C and Iso-G in the design of b-DNA probes, these background issues were "practically negated".**

September 8, 2000

Applied Biosystems

850 Lincoln Centre Drive
Foster City, CA 94404 U.S.A
T 650.570.6667 F 650.572.2743
www.appliedbiosystems.com

**By Priority Mail**

Ann M. Caviani Pease, Esq.
Pennie & Edmonds LLP
3300 Hillview Avenue
Palo Alto, California 94304

Re: New United States Patent Application
For: **USE OF AEGIS BASES FOR DECODING (AND BEYOND)**
By: Gary P. Schroth
Your Case No.: to be assigned
Our Case No.: 4617 US

Dear Ann:

As we discussed, enclosed is a copy of an invention disclosure. Please prepare a patent application for this matter.

Very truly yours,

Scott/pds

Scott R. Bortner, Ph.D.
Senior Patent Attorney, Applied Biosystems

Enclosures

::ODMA\MHODMA\imanage;23407;1

# PENNIE & EDMONDS LLP

NEW YORK OFFICE
1155 AVENUE OF THE AMERICAS
NEW YORK, NEW YORK 10036
(212) 790-9090
FACSIMILE: (212) 869-9741/8864

3300 HILLVIEW AVENUE
PALO ALTO, CALIFORNIA 94304
(650) 493-4935
FACSIMILE: (650) 493-5556
MCI MAIL: 561-3768

WASHINGTON OFFICE
1667 K STREET, N.W.
WASHINGTON, DC 20006
(202) 496-4400
FACSIMILE: (202) 496-4444

WRITER'S DIRECT DIAL:
(650) 849-7607

INTERNET ADDRESS:
PATHAKR@PENNIE.COM




February 15, 2001

**By First Class Mail**

009584-0030-999

Scott Bortner, Esq.
PE Biosystems
850 Lincoln Centre Drive
Foster City, CA 94404

Re: Draft United States Patent Application
Entitled: METHODS OF USING UNNATURAL NUCLEOBASES FOR DECODING
Inventor: Gary P. Schroth
Our Ref.: 9584-0030-999

Dear Scott:

Enclosed is a draft of a patent application in relation to the captioned matter. Please review the draft application to ensure that: (1) it is accurate and complete; (2) it sets forth sufficient detail to enable those skilled in the art to build and use the invention; and (3) the best mode of practicing the invention, i.e., the preferred way of constructing and using the invention, is disclosed. Prompts where additional information is needed are in bold type.

We look forward to receiving your comments and filing the application.

Very truly yours,

Rahul Pathak

Enclosure

cc: Samuel B. Abrams, Esq.
Ann M. Caviani Pease, Esq.

# PENNIE & EDMONDS LLP

NEW YORK OFFICE
1155 AVENUE OF THE AMERICAS
NEW YORK, NEW YORK 10036
(212) 790-9090
FACSIMILE: (212) 869-9741/8864

3300 HILLVIEW AVENUE
PALO ALTO, CALIFORNIA 94304
(650) 493-4935
FACSIMILE: (650) 493-5556
MCI MAIL: 561-3768

WASHINGTON OFFICE
1667 K STREET, N.W.
WASHINGTON, DC 20006
(202) 496-4400
FACSIMILE: (202) 496-4444

WRITER'S DIRECT DIAL:
(650) 849-7607

INTERNET ADDRESS:
PATHAKR@PENNIE.COM



July 6, 2001

**By First Class Mail**

009584-0030-999

Scott Bortner, Esq.
PE Biosystems
850 Lincoln Centre Drive
Foster City, CA 94404

Re: Draft Patent Application
Entitled: METHODS OF USING UNNATURAL NUCLEOBASES FOR DECODING
Inventor: Gary P. Schroth
Our Ref.: 9584-0030-999

Dear Scott:

Enclosed is a revised draft of a patent application in relation to the captioned matter.

The draft has been revised in accordance with our recent conversation about the application. Prompts where additional information is still needed are in bold type.

Please review the draft application to ensure that: (1) it is accurate and complete; (2) it sets forth sufficient detail to enable those skilled in the art to build and use the invention; and (3) the best mode of practicing the invention, i.e., the preferred way of constructing and using the invention, is disclosed.

We look forward to receiving your comments and filing the application.

Very truly yours,

Rahul Pathak

Enclosure

cc: Samuel B. Abrams, Esq.

F

# PENNIE & EDMONDS LLP

NEW YORK OFFICE
1155 AVENUE OF THE AMERICAS
NEW YORK, NEW YORK 10036
(212) 790-9090
FACSIMILE: (212) 869-9741/8864

3300 HILLVIEW AVENUE
PALO ALTO, CALIFORNIA 94304
(650) 493-4935
FACSIMILE: (650) 493-5556
MCI MAIL: 561-3768

WASHINGTON OFFICE
1667 K STREET, N.W.
WASHINGTON, DC 20006
(202) 496-4400
FACSIMILE: (202) 496-4444

WRITER'S DIRECT DIAL:
(650) 849-7607

INTERNET ADDRESS:
PATHAKR@PENNIE.COM



July 18, 2001

**By First Class Mail**

009584-0030-999

Scott Bortner, Esq.
PE Biosystems
850 Lincoln Centre Drive
Foster City, CA 94404

Re: Revised Draft Patent Application
Entitled: METHODS OF USING UNNATURAL NUCLEOBASES FOR DECODING
Inventor: Gary P. Schroth
Our Ref.: 9584-0030-999

Dear Scott:

Enclosed is a revised draft of a patent application along with copies of the figures in relation to the captioned matter.

The draft has been revised in accordance with our recent conversation about the application. Prompts are for the inventors where additional information is still needed are in bold type.

Please review the draft application to ensure that: (1) it is accurate and complete; (2) it sets forth sufficient detail to enable those skilled in the art to build and use the invention; and (3) the best mode of practicing the invention, i.e., the preferred way of constructing and using the invention, is disclosed.

We look forward to receiving your comments and filing the application.

Very truly yours,

Rahul Pathak

Enclosure

cc: Samuel B. Abrams, Esq.

Applied Biosystems
an Applera Corporation Business

850 Lincoln Centre Drive
Foster City, CA 94404-1128 U.S.A.
T. 650 570 6667 F. 650 572 2743
www.appliedbiosystems.com



October 3, 2001

**By Priority Mail**

Rahul Pathak, Esq.
Pennie & Edmonds LLP
3300 Hillview Avenue
Palo Alto, California 94304

Re: New U.S. Patent Application
For: **METHODS OF USING UNNATURAL NUCLEOBASES FOR DECODING**
Your Ref. No.: 9584-030-999
Our Ref. No.: 4617 US

Dear Rahul:

Enclosed is a copy of the above application with Gary Schroth's comments written in blue. Comments in photo-copy black are from Scott Bortner. Please call Dr. Bortner at 650-638-6245 with any questions regarding the application.

Very truly yours,

Patti D. Selan
Patent Administrator, Applied Biosystems

Enclosures

# PENNIE & EDMONDS LLP

NEW YORK OFFICE
1155 AVENUE OF THE AMERICAS
NEW YORK, NEW YORK 10036
(212) 790-9090
FACSIMILE: (212) 869-9741/8864

3300 HILLVIEW AVENUE
PALO ALTO, CALIFORNIA 94304
(650) 493-4935
FACSIMILE: (650) 493-5556
MCI MAIL: 561-3768

WASHINGTON OFFICE
1667 K STREET, N.W.
WASHINGTON, DC 20006
(202) 496-4400
FACSIMILE: (202) 496-4444

WRITER'S DIRECT DIAL:
(650) 849-7607

INTERNET ADDRESS:
PATHAKR@PENNIE.COM




December 20, 2001
**By Federal Express**

Scott Bortner, Esq.
PE Biosystems
850 Lincoln Centre Drive
Foster City, CA 94404

Re: Revised Draft Patent Application
Entitled: METHODS OF USING UNNATURAL NUCLEOBASES FOR DECODING
Inventor: Gary P. Schroth
Our Ref.: 9584-0030-999

Dear Scott:

Enclosed is a revised draft of a patent application along with copies of the figures in relation to the captioned matter.

The draft has been revised in accordance with our recent conversation about the application.

Please review the draft application to ensure that: (1) it is accurate and complete; (2) it sets forth sufficient detail to enable those skilled in the art to build and use the invention; and (3) the best mode of practicing the invention, i.e., the preferred way of constructing and using the invention, is disclosed.

We look forward to receiving your comments and filing the application.

Very truly yours,

Rahul Pathak

Enclosure

cc: Samuel B. Abrams, Esq.

Pennie & Edmonds LLP
ATTORNEYS-AT-LAW

3300 HILLVIEW AVENUE
PALO ALTO, CALIFORNIA 94304-1203
(650) 493-4935
FACSIMILE (650) 493-5556

**NEW YORK**
1155 AVENUE OF THE AMERICAS
NEW YORK, NY 10036-2711
(212) 790-9090
FACSIMILE: (212) 869-8864/9741

**WASHINGTON, D.C.**
1667 K STREET, N. W.
WASHINGTON, D.C. 20006-1605
(202) 496-4400
FACSIMILE: (202) 496-4444

WRITER'S DIRECT DIAL:
(650) 849-7607
INTERNET ADDRESS:
RRP@PENNIE.COM

March 5, 2002



**By First Class Mail**

Ms. Patti Selan
PE Biosystems
850 Lincoln Centre Drive
Foster City, CA 94404

Re: U.S. Patent Application
Filed: March 1, 2002
Entitled: METHODS OF USING UNNATURAL NUCLEOBASES FOR DECODING
Inventor: Gary P. Schroth
Our Ref.: 9584-0030-999

Dear Patti:

Enclosed for your files, please find a copy of the utility patent application that we filed on your behalf in the United States Patent & Trademark Office on March 1, 2002.

At this point, we would like to remind you that, pursuant to 37 C.F.R. §1.56, "[e]ach individual associated with the filing and prosecution of a patent application has a duty of candor and good faith in dealing with the Patent and Trademark Office, which includes a duty to disclose to the Office all information known to that individual to be material to patentability as defined in this section." Such an individual typically can be, for example, an applicant, an assignee, an attorney or an agent handling the proceedings in both the U.S. and foreign corresponding applications.

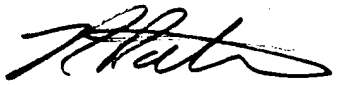
Please note that under 37 C.F.R. §1.97, there are time constraints and conditions regarding the submission of a reference to the Examiner. If the requirements are not met, then the Patent and Trademark Office (PTO) can require a fee as well as a petition requesting that the reference be considered. Under some circumstances, the PTO may prohibit the reference from being considered.

Typically, an Information Disclosure Statement filed after three months from the filing date of the application may be subject to fees under the rules. Also, in order to be considered by the PTO, all references disclosed which are not in the English language should be accompanied by a concise explanation of their relevance.

This duty to disclose continues after the filing of the application, such that any material information which later becomes known, such as art cited in any co-pending applications or corresponding foreign applications, should similarly be disclosed to the PTO. This duty to disclose extends through to the issuance of the patent of the present application and into any continuation applications. Thus, please provide us with any references which you believe are material to the newly filed application.

We will keep you informed of further developments in this case as they occur. In the meantime, if you have any questions or concerns regarding this matter, please do not hesitate to contact us.

Very truly yours,



Rahul Pathak

Enclosure

cc: Samuel B. Abrams, Esq.